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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/068,751	11/02/1998	WOLFGANG-M. FRANZ	690-110PCT	2640

2292 7590 07/29/2004

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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 07/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/068,751	FRANZ ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *83-121* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *83-92 and 95-121* is/are rejected.

7)☒ Claim(s) *93 and 94* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 November 1998* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communications filed 4-30-04.

Claims 83-121 are pending in the instant application.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Figures in the Application

Figure 10 is missing from the specification. Applicant is required to furnish a figure under 37 CFR 1.81. No new matter may be introduced in the required figure.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

New Rejections

The incorporation of essential material in the specification by reference to a foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing

application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

The attempt to incorporate subject matter into this application by reference to the citation of Stratford-Perricaudet et al (page 15, last paragraph of the instant specification) is improper because the essential subject matter has not been included in the instant specification which describes the synthesis of the pADRSVβ-gal vector. The pADRSVβ-gal vector is required to practice the invention as described in claim 85, which involves insertion of mlc-2 promoter fragments into the pADRSVβ-gal vector. Applicants may overcome this rejection by amending the specification to include the material incorporated by the reference of Stratford-Perricaudet, L. D. et al, which describes the construction of this vector (J. Clinical Invest. 90: 626-630, 1992, second paragraph of the Methods section, on page 626). This amendment must be accompanied by an affidavit or declaration executed by the applicant, or representative thereof, stating that the amendatory material consists of the same material incorporated by reference in the referencing application (see MPEP 608.01(p)).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 91, 92, 95-97, 101-103, 107-109, 113-115, 119-120 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The metes and bound of the term "repeat sequences" in claim 91, line 4, cannot be determined, since it reads broadly on any sequences that repeat and that are found in a lentivirus, adenovirus or AAV recombinant vector. The specification and other claims of the invention, however, recite recombinant viral vectors comprising inverted terminal repeat sequences, which are known in the art (e.g. inserting –terminal— before "repeat" would be remedial).

The declarations under 37 CFR 1.132 filed 6-28-02 and 7-15-02 are insufficient to overcome the rejection of claims 83-92, 95-121 based upon lack of enablement over the scope claimed. Applicants argue that the scope of the claimed invention is enabled for recombinant viral vectors that include lentivirus, as well as adeno- and AAV derived recombinant vectors. The declarations, while generally stating that recombinant viral vectors can be constructed over the scope claimed, specifically address the regulatory components of the mammalian mlc-2 gene that are incorporated into the recombinant viral vectors taught in the specification, which viral vectors comprise adeno-derived recombinant viral vectors, and not lentiviral vectors. The declarations also elaborate on the working examples of the invention that are illustrated in the specification, and teach cardiac expression using adenoviral recombinant vectors. Contrary to Applicants' assertion in the declarations that viral vectors are generally enabled, including lentiviral

recombinant vectors further comprising the mammalian mlc-2 promoter, no examples have been provided in the specification or in the declarations concerning construction of lentiviral recombinant vectors. Lentivirus derived recombinant viral vectors were not well characterized in the art at the time the invention was made, and this aspect of the claimed invention is addressed in the 112, first paragraph rejection, for lacking scope of enablement, set forth below.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 83-92, 95-121 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a recombinant adenoviral, adeno-associated viral or replication deficient adeno-virus vector comprising two terminal repeat sequences of said viruses and packaging signal of said viruses, and a functional mammalian myosin light chain-2 gene derived promoter fragment corresponding to nucleotides of residue –19 to approximately residue –2700 with respect to the transcription starting point (e.g. nucleotide 2406 of SEQ ID NO: 1), or as described as the regulatory elements in claim 91, and being enabled for delivery of this vector to cardiac muscle cells of a subject, does not reasonably provide enablement for a recombinant lentivirus vector comprising two terminal repeat sequences of said virus and packaging signal of said virus, nor for a recombinant viral vector comprising any fragment of the mammalian myosin light chain-2 gene derived promoter. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to compositions and methods of delivering to cardiac muscle in a subject a recombinant virus vector that is a lentivirus vector, adenovirus vector, adeno-associated or replication deficient adeno-virus vector comprising two terminal repeat sequences, a packaging signal of said virus, and a promoter nucleic acid fragment of mammalian myosin light chain-2 gene.

The state of the prior art and the predictability or unpredictability of the art. Palu et al teach that the success of gene delivery using virally derived vectors is dependent on the empirical determination of successful gene transduction for a given vector and a given target cell (See entire article, especially page 4, section 2.) In addition, Peracchi cites stability and delivery obstacles that need to be overcome in achieving desired in vivo efficacy of nucleic acids: "A crucial limit of ribozymes in particular, and of oligonucleotide-based drugs in general, lies in their intrinsically low ability to cross biological membranes, and therefore to enter the cells where they are supposed to operate...cellular uptake following systemic administration appears to require more sophisticated formulations... the establishment of delivery systems that mediate efficient cellular uptake and sustained release of the ribozyme remains one of the major hurdles in the field." (See text on page 51).

Cellular uptake of nucleic acids by appropriate target cells is a rate limiting step that has yet to be overcome in achieving predictable clinical efficacy using

oligonucleotides. Both Chirila et al and Agrawal et al point to the current limitations which exist in our understanding of the cellular uptake of nucleic acids in vitro and in vivo (see Agrawal et al especially at pages 79-80; see Chirila et al in its entirety, especially pages 326-327 for a general review of the "important and inordinately difficult challenge" of the delivery of therapeutic nucleic acids to target cells).

Lentiviral biology was still in its infancy at the time the invention was made. Lentiviruses include, among others, HIV, SIV and EIAV, whose viral components were the object of much investigation at the time the instant invention was made (see e.g. Rosin-Argesfeld et al. Gene 150: 307-311 , 1994; Kent et al. AIDS Res. and Human Retroviruses 10(5): 551-560, 1994); Naldini, L. et al. Science 272(5259) : 263-268, 1996). The utilization of various lentiviral components for the construction of retroviral vectors required undue experimentation beyond that provided in the instant disclosure and the art at the time the invention was made, for the various components of different lentiviruses were not found to be analogous or interchangeable (e.g. see the abstract of Rosin-Arbesfeld: "The recombinant Tat protein was shown to potently trans-activate the EIAV long terminal repeat (LTR) following the introduction into canine cells by 'scrape loading.' The EIAV Tat protein was found to localize predominantly within the cytoplasm, in contrast to HIV-1 Tat." See also Kent et al on page 599: "Reproducible methods of defining lentivirus-specific CTL responses in macaques, independent of MHC genotype and the previous immunological history of the host, are essential for the elucidation of lentivirus biology.")

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. Applicants have not provided guidance in the specification toward a method of making or using a recombinant virus vector that is a lentivirus vector, nor of making or using any recombinant viral victor using any fragment of the mammalian myosin light chain-2 gene. The specification teaches methods of making a recombinant adenoviral or adeno-associated viral vector comprising two terminal repeat sequences of said viruses and packaging signal of said viruses, and a functional mammalian myosin light chain-2 gene derived promoter fragment corresponding to nucleotides of residue –19 to approximately residue –2700 with respect to the transcription starting point (e.g. nucleotide 2406 of SEQ ID NO: 1), and its delivery to cardiac muscles in a subject. The specification fails to teach methods of making any recombinant lentivirus vector or its delivery to the cardiac muscle in a host. One skilled in the art would not accept on its face the examples given in the specification of the adeno-derived recombinant viral vector and its delivery to cardiac muscle as being correlative or representative of lentiviral vectors in view of the lack of guidance in the specification and known unpredictability associated with the ability to construct recombinant lentiviral vectors and deliver them to cardiac muscle in a subject.
The breadth of the claims and the quantity of experimentation required. The claims are drawn to compositions and methods of delivering to cardiac muscle in a subject a recombinant virus vector that is a lentivirus vector, adenovirus vector, or adeno-associated virus vector comprising two inverted terminal repeat sequences, a packaging signal of said virus, and a promoter nucleic acid fragment of mammalian

myosin light chain-2 gene. The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of the various viral components of a representative number of lentiviral family members, whereby recombinant lentiviral vectors are constructed that allow cardiac specific delivery and expression of subcloned and operably linked nucleic acids driven by the mammalian mlc-2 promoter. This would require controlling lentiviral infectivity by removing identified and relevant portions of the lentiviral genome so that target (cardiac muscle) delivery is obtained in an organism and lentiviral infectivity is controlled. The generation of recombined lentiviruses comprising deletion of appropriate regions of the lentiviral genome (e.g. including identification within the various lentiviral genomes of regions corresponding to the E1 and E3 regions of the previously characterized adenoviruses), as well as identification of the crucial ITR and packaging sequences for generating functional, recombinant lentiviral vectors for targeted gene delivery in a subject (for a representative number of lentiviruses), as has been accomplished for adenoviral vectors (e.g. see page 17, § 2 of the instant spefication), would require undue experimentation beyond that taught in the instant specification, or known in the art at the time the invention was made. Since the specification fails to provide any particular guidance for making lentivirus recombinant vectors, deleting appropriate parts of the lentivirus genome, controlling lentivirus infectivity after infecting with lentivirus recombinant vector, utilizing the crucial terminal repeat and packaging sequences in a recombinant retroviral construct, or subcloning and expressing heterologous recombinant polypeptides, and further whereby delivery to cardiac muscle is achieved, and since determination of

these factors for a particular lentivirus and for a representative number of lentiviruses is highly unpredictable, it would require undue experimentation to practice the invention over the scope claimed.

Allowable Subject Matter

Claims 93 and 94 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is **703-872-9306**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (571) 272-0760. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JZ

7-12-04

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